Comments Related to Rodent Bioassays and Breast Cancer Prevention

Submitted to Dr. Paul Foster in anticipation of the workshop:
"Hormonally-Induced Reproductive Tumors: Relevance of Rodent Bioassays"
National Toxicology Program, May 22, 2006

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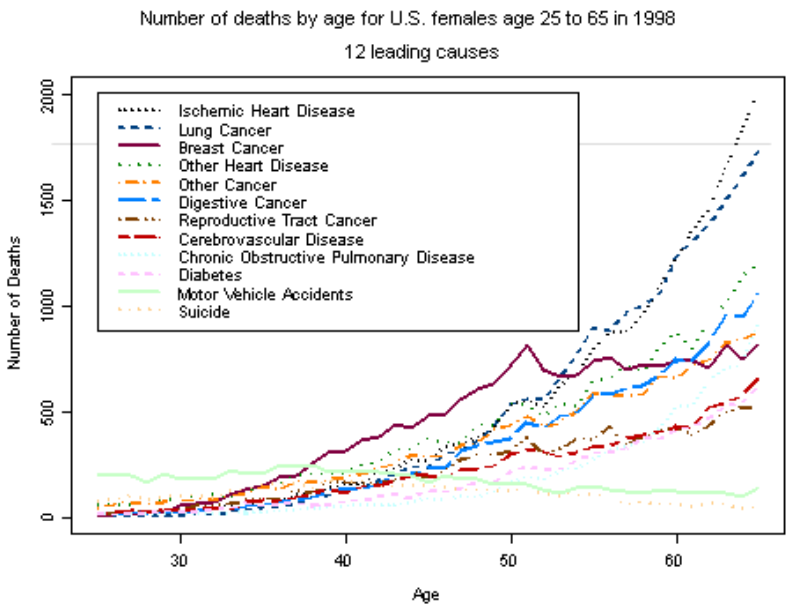
Summary: Breast cancer is an urgent public health problem and cancer bioassays provide an opportunity to prevent some cases by directing policies to limit exposure to carcinogens. We identified 221 chemicals that have been shown to induce mammary gland tumors in animal studies, but most chemicals in use have not been tested. Almost all of the mammary gland carcinogens we identified were mutagenic and most caused tumors in multiple organs and species; these characteristics are generally thought to indicate likely carcinogenicity in humans. Some characteristics of the bioassay lead to challenges in interpreting results for mammary gland tumors. Perhaps due to these difficulties in interpretation, risk assessments used as the basis for regulation often do not mention mammary gland tumors or breast cancer, even where it may be relevant. Priority needs include (1) improved integration of mammary gland tumor data into risk assessment and regulatory documents, and (2) careful evaluation of existing and new or modified testing programs in terms of their ability to identify potential breast carcinogens.

Breast cancer is an urgent public health problem and cancer bioassays provide an opportunity to prevent some cases by directing policies to limit exposure to carcinogens

Breast cancer is the most common invasive cancer in women. Although screening and treatment have contributed to declining US mortality, breast cancer is the leading cause of death in women from their late thirties to mid fifties, years when they are raising children and making primary contributions to work and communities (see Figure 1) (National Center for Health Statistics 2006). While we hope and expect that



survival will continue to improve, treatment is likely to remain strenuous and debilitating for the foreseeable future, with potential ancillary effects on cardiovascular health, secondary cancers, physical mobility, cognition, sexuality, and social factors. Financial costs of treatment are substantial. In this context, research with a goal of breast cancer prevention should be a major public health priority alongside research into screening and treatment.

Human carcinogens have largely been identified in occupational studies, but these provide little information on women's cancers since most of the studied populations have been male. Experimental studies in animals offer an alternative means for identifying potential carcinogens and are a key source of information, given that epidemiologic studies require a large number of women, a long duration, and substantial—often-unattainable—exposure information. Animal models of chemically induced cancer are currently the primary means of understanding and anticipating effects of chemicals in humans. All known human carcinogens that have been tested in animals are also carcinogenic in animal models, and there is at least one common organ site in both species (Huff 1993; Huff 1999; Huff and Melnick 2006). Target organs for carcinogens are not necessarily the same across species, so while it is likely that chemicals that cause mammary tumors in rats will also cause tumors in some organ in mice, the mammary gland is not necessarily going to be the target in both species (Gold et al. 1991). Nevertheless, the animal bioassay to evaluate chemically-induced mammary gland tumors is the only tool currently available to help anticipate and prevent exposure to chemical breast carcinogens.

We identified 221 chemicals that have been shown to induce mammary gland tumors in animal studies, but most chemicals in use have not been tested

We identified 221 chemicals that have been associated with increased mammary gland tumors in animal studies (Gold et al. 1991; Gold LS 2005; International Agency for Research on Cancer (IARC) 2005; National Toxicology Program: Department of Health and Human Services 2005; National Toxicology Program: Department of Health and Human Services 2005; Toxicology Data Network (Toxnet): National Library of Medicine). Of the 221 chemicals on the list, 28 are produced in the US at > 1 million pounds/year, 36 are likely air pollutants, 25 involve occupational exposures to greater than 5000 women, 10 are registered with FDA as food additives, and 67 are or have historically been present in consumer products or as contaminants of food. Thus, exposure is widespread. Details of our methods and the list of mammary gland carcinogens will be published in the next few months.

Our list of 221 mammary gland carcinogens is incomplete because the carcinogenic potential of most chemicals is not known because it has not been evaluated. The full two-year cancer bioassay run by the US NTP costs about $2 million and uses about 800 animals. While the NTP has tested about 500 chemicals using this bioassay, and data suggest that other organizations may have tested about 500 additional chemicals in similar types of tests (Huff 1993), there are 80,000 chemicals registered by US EPA as in commercial use, and of these about 3,000 are produced at > 1 million pounds per year. Even data on mutagenicity, which can be an indicator of carcinogenic potential of chemicals and can be evaluated in some tests for as little as

$5000, is lacking; in a 1999 analysis US EPA has mutation data for only 33% of the HPV chemicals (US Environmental Protection Agency 1999).

Almost all of the 221 mammary gland carcinogens we identified were mutagenic and most caused tumors in multiple organs and species; these characteristics are generally thought to indicate likely carcinogenicity in humans

Not all chemicals that induce mammary gland tumors in animals are equally carcinogenic or represent a significant risk to humans. The 221 chemicals we listed vary in the strength of the evidence that they are likely to be human carcinogens, and each has to be evaluated with respect to potency, dose-response, target sites, tumor incidence, multiplicity (number of tumors per animal), latency, and exposure routes and levels in humans (Wolff et al. 1996). Although we did not evaluate the strength of evidence for carcinogenicity for each chemical in our list, 88 of the 117 chemicals that were reviewed by IARC meet the IARC criteria for "sufficient" evidence of carcinogenicity in animals. This is consistent with our observation that many of the chemicals cause tumors at other sites as well, and cause tumors in both mice and rats. In fact, an analysis by Gold et al. (Gold et al. 1991) showed that 91% of chemicals from Carcinogenic Potency Data Base that were mammary tumorigens in rats also caused tumors at some site in mice, and that 89% of chemicals that caused mammary gland tumors in mice also caused tumors at some site in rats. Taken together with the fact that the chemicals in our list are overwhelmingly positive for mutagenic activity (84% with some evidence of mutagenicity, 11% with some evidence of lack of mutagenicity, 5% with no data), it is reasonable to expect from this preliminary assessment that many of them are potential human carcinogens, even at the lower exposure levels expected in humans.

Some characteristics of the bioassay lead to challenges in interpreting results for mammary gland tumors

Some characteristics of the mammary tumor endpoint raise challenging issues in interpreting study results. Issues include:

- inconsistencies in the interpretation of whether treatment-related fibroadenomas (a common benign tumor in rat models) are likely to progress to malignancy;
- lack of sensitivity of the rat model because of the "noise" due to high and variable background rates of fibroadenomas;
- inappropriate use of higher background tumor rates in controls from other studies to discount increased tumors compared with concurrent controls;
- limited understanding of rodent/human differences in hormonal influences on mammary gland tumors, especially the role of prolactin (see Russo and Russo (1996) and Harvey (2005) for reviews);
- the influence of treatment-related weight loss on dose-response for mammary gland tumors given that mammary tumor rates are higher in heavier animals and high dose groups often experience weight loss; and

- the impact of survival problems and short study duration on sensitivity to mammary gland tumors, since these tumors usually develop late in the test.

Perhaps due to these difficulties in mammary gland tumor interpretation, risk assessments used as the basis for regulation often do not mention mammary gland tumors or breast cancer, even where it may be relevant

Controversies in the interpretation of the mammary tumor endpoint appear to result in a lack of attention to mammary tumors and to breast cancer in chemical risk assessments that are the basis for environmental policies and regulations. As previously mentioned, most of the chemicals that we identified as mammary gland carcinogens also cause tumors at other sites. In our review we found that most risk assessment and regulatory documents related to these chemicals focus on the other sites, often never mentioning the mammary gland tumors or potential for breast cancer. For example:

- US EPA uses animal tumor data to calculate estimates of the potency of carcinogens, so that estimated cancer risks can be calculated for various exposure scenarios. Of the (only!) 20 chemicals on our list of 221 mammary gland carcinogens for which US EPA has calculated potency factors, the mammary gland tumors are the basis for the potency calculation for only two chemicals (acrylamide and 3,3-dichlorobenzidine) (US EPA 2005). This may reflect the chemical being more potent for sites other than mammary gland, and/or that interpretation of dose-response data for the mammary gland endpoint was complicated.
- NIOSH has developed standardized information on potential workplace chemical hazards. Of the 30 chemicals on our list identified by NIOSH as potential occupational carcinogens, only 7 include mammary gland tumors in the list of target sites in animals (National Institute for Occupational Safety and Health 2004). This is important because the information from NIOSH is often the primary source of information about potential exposure-related health effects for workers, their health and safety officers, and their physicians.
- Similarly, OSHA requires medical surveillance for workers exposed to 11 of the chemicals on our list, but none of these requirements include breast cancer screening (National Institutes for Occupational Safety and Health 1990).
- Diesel exhaust, which contains mammary gland carcinogens such as PAHs and nitroPAHs, has garnered extensive regulatory attention, and there are many comprehensive health assessment-type documents characterizing potential risks, however none of these mentions mammary gland tumors or breast cancer. Similarly, the drinking water disinfection by-product known as MX causes mammary gland tumors but risk assessment and regulatory documents related to drinking water disinfection focus on cancers of the gastro-intestinal tract and do not mention breast cancer.

Priority data needs include (1) improved integration of mammary gland tumor data into risk assessment and regulatory documents, and (2) careful evaluation of existing and new or modified testing programs in terms of their ability to identify potential breast carcinogens

Because the animal cancer bioassay is the only real tool available to identify chemicals that might increase risk of breast cancer, it is essential that it be an effective tool.

A first priority is to clarify the issues that affect integration of the rodent bioassay data on mammary gland tumors into risk assessment and regulatory documents. This may include, for example, working with EPA and other risk assessors to develop guidelines on interpretation of mammary gland tumor data from the bioassay and application of these data to risk assessments. This process may help determine whether the existing bioassay is a sensitive tool but the risk assessment process does not adequately integrate this information, or whether the bioassay has some weaknesses that make it not a useful tool for identifying potential breast carcinogens.

Second, a careful evaluation of existing and new or modified testing programs in terms of their ability to identify potential breast carcinogens is a priority. Screening and testing methods need to be sensitive and reliable. Rodent strains typically used for carcinogenesis bioassays may not be optimal for identifying mammary carcinogens, because of either a reduced susceptibility to such tumors, such as in B6C3F1 mice, or because a high background rate of mammary tumors in Fisher 344 rats makes results difficult to interpret (Bennett and Davis 2002; Dunnick et al. 1995). While the animal models used by NTP and others have identified a large number of potential breast carcinogens, limitations of these models have made interpretation and risk assessment weak with respect to this endpoint. However, these models have some strengths (Russo and Russo 1996), and it will be important to consider new alternatives carefully.

The adequacy of existing and potentially modified testing programs must also be evaluated with respect to the critical role of timing of exposure on tumors of the mammary gland and other hormonally-mediated tissues. For example, current protocols do not adequately address increased susceptibility to carcinogens due to early-life exposures, because dosing typically begins in pubertal animals. In addition, bioassays must be able to identify chemicals that affect mammary gland susceptibility to carcinogenesis, especially following in utero exposure (Birnbaum and Fenton 2003; Brody and Rudel 2003).

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